Neuronal synchrony: peculiarity and generality

Article (Published Version)

Neuronal synchrony: Peculiarity and generality

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(Received 5 March 2008; accepted 2 June 2008; published online 22 September 2008)

Synchronization in neuronal systems is a new and intriguing application of dynamical systems theory. Why are neuronal systems different as a subject for synchronization? (1) Neurons in themselves are multidimensional nonlinear systems that are able to exhibit a wide variety of different activity patterns. Their "dynamical repertoire" includes regular or chaotic spiking, regular or chaotic bursting, multistability, and complex transient regimes. (2) Usually, neuronal oscillations are the result of the cooperative activity of many synaptically connected neurons (a neuronal circuit). Thus, it is necessary to consider synchronization between different neuronal circuits as well. (3) The synapses that implement the coupling between neurons are also dynamical elements and their intrinsic dynamics influences the process of synchronization or entrainment significantly. In this review we will focus on four new problems: (i) the synchronization in minimal neuronal networks with plastic synapses (synchronization with activity dependent coupling), (ii) synchronization of bursts that are generated by a group of nonsymmetrically coupled inhibitory neurons (heteroclinic synchronization), (iii) the coordination of activities of two coupled neuronal networks (partial synchronization of small composite structures), and (iv) coarse grained synchronization in larger systems (synchronization on a mesoscopic scale). © *2008 American Institute of Physics*.
[DOI: 10.1063/1.2949925]

The observation of synchrony (coherence, correlation) in the brain and the entire nervous system has a long history. Neuronal synchronization has been experimentally analyzed on many different levels of system complexity. Even though the functional role of this phenomenon is still not absolutely clear, neuroscientists agree that the level of synchrony is one of the key characteristics of the activity of the brain/neuronal systems in general. Both limit cases, too strong and too weak synchronization are characteristic for certain brain disorders, such as epilepsy, Parkinson's disease, Alzheimer's disease, and schizophrenia (see Refs. 1 and 2). In this short review we discuss a few mechanisms of neuronal synchronization that illustrate the specificity of the corresponding phenomena in neuronal circuits, and their similarity to classical examples in physical systems. We also discuss briefly the influence of the complexity of real neuronal systems on synchronous dynamics.

I. INTRODUCTION: THE FUNCTIONAL ROLE OF NEURONAL SYNCHRONIZATION

The question "Does synchronization in the brain really play a key role in controlling behavior and cognition or is it just an epiphenomenon that accompanies the cooperative information processing by huge numbers of neurons in the brain?" has been the focus of numerous intensive discussions[3–7] and still has no convincing answer. However, many fascinating experiments have revealed synchronization (coherence or correlation) within and between different parts of the brain. These experiments have suggested a lot of interesting hypotheses about the functional role of synchronization in the brain, but verifying them *in vivo* has remained difficult due to the intricacies of exerting sufficient experimental control to change some control parameters while keeping others precisely constant. A promising alternative approach to solve this dilemma, at least partially, is to resort to dynamical models of how the brain executes specific functions depending on environmental conditions.

A. Background

More than 30 years ago the popular binding hypothesis regarding the role of synchronization in sensory brain areas was formulated.[8–11] According to this hypothesis, the oscillatory synchronization of activity in different brain regions subserves the perceptual and cognitive function of associating ("binding together") different sensory or cognitive aspects of an object (reflected in concurrent activities in different neuron populations). The requirement of synchrony arises from the need to prevent illusory conjunctions of responses that are elicited concurrently but are otherwise unrelated.[12] The gamma-band phase synchronization is the most accepted mechanism for informational integration by synchronization across different brain areas.[4–6,13,14]

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The binding hypothesis has been criticized because of the difficulties in explaining how downstream brain areas can distinguish meaningful mutual synchronization between neurons from accidental co-occurence of spikes.[15] Modeling efforts have suggested that this problem may be circumvented by self-organization through short-term plasticity.[16] Nevertheless, the binding hypothesis remains controversial but there is also no accepted alternative hypotheses on how to avoid the illusory conjunction problem.

Experimental evidence for the involvement of synchronization in sensory information processing and coordination of activities of different brain regions comes from recent observations in behavioral studies. For example, Fell and collaborators[17] observed, based on the intracranial electroencephalograms from human rhinal cortex and hippocampus, that the level of synchronization was greater while subjects learned a word later remembered than when trying to learn words later forgotten. The authors hypothesize that increased gamma phase coupling may reflect a change in the functional connectivity between rhinal and hippocampal regions that is important for memory formation. Similar effects have been observed in rats that are subjected to a hard decision problem. If a rat has to choose between two very similar choices, the gamma frequency band elevates its power dramatically.[18] While this is not a direct proof of the relevance of gamma band oscillations for information processing in the brain it certainly shows their critical involvement. Furthermore, both observations are consistent with the evidence linking synchronization of brain regions to attention.[7,19–24]

Long-range synchronization has also been intensively investigated in the neuronal circuits related to the control of motor behavior. The main hypothesis here is, however, quite different: Abnormally increased synchronization or abnormal patterns of synchronization in motor systems may be causing pathologies such as tremors and Parkinson's disease.[3]

B. Subject of the review

It is possible to multiply the number of interesting hypotheses about the functional role of neuronal synchronization beyond the classic examples mentioned above. While these intriguing ideas certainly motivate us to have a closer look at neuronal synchronization phenomena, we will leave the question of functional roles aside for now and focus this review on the more concrete question whether and why neuronal systems may be unusual as a subject for synchronization.

Is it just because neuronal systems are very complex; i.e., have huge numbers of oscillators and complex connectivities? Or are there other reasons?

To approach this question we have to remind some specific features of neuronal systems, in addition to network complexity:

(i) Neurons themselves are multidimensional nonlinear systems that are able to exhibit a variety of different activities. These encompass tonic spiking, regular or chaotic bursting, multistability, and complex transient regimes.

(ii) Usually, neuronal oscillations are the result of the cooperative activity of many synaptically connected circuits. Thus, it is necessary to consider synchronization between different neuronal circuits in addition to the synchronization of individual neurons.

(iii) Synapses are dynamical systems in their own right and influence the process of synchronization or entrainment significantly.

(iv) In the brain, spatio-temporal information is embedded in oscillations that exist at many different scales in space and time. In space it can be synchronization of individual neurons, small groups of neurons or small cortical areas, or, at the other end of the scale, global brain synchronization that includes both hemispheres. The same applies with respect to time: brain rhythms (temporal scales) cover a wide range of time scales from 5 ms (200 Hz sharp-wave ripples)[25] to 10 s (sleep waves and cognitive rhythms).[26]

(v) In neuronal systems a new control parameter appears—the size of the neuronal population that is subject to synchronization. For example, Bibbig and collaborators[27] have shown that the frequency of the entrainment of a neuronal population in the hippocampus can depend on the level of recruitment of neurons in the process of synchronization. They observed that in conditions in which only very few cells are recruited in the oscillations, the population rhythm has a frequency in the gamma band (30–80 Hz). However, if the recruitment of cells was enhanced by application of a neurotransmitter, the network generated a slower beta-frequency (12–20 Hz) oscillation as a near-subharmonic of the forcing gamma rhythm.

(vi) In many cases the synchronization in neuronal systems is transient. It is important to remember that nearly all cognitive processes in the brain are transient; i.e., that most behavioral and cognitive functions of the brain correspond to a stimulus-dependent or spontaneous succession of global brain states and rapid transitions between them. Recently, Gervasoni and collaborators[28] proposed that transient oscillatory synchronization is one potential dynamical mechanisms for the rapid switching of brain states. They presented direct evidence that global state transitions occur simultaneously across multiple forebrain areas in form of drastic changes in neuronal synchronization. They also hypothesize that such transient synchronization events may facilitate the exchange of information within and across brain areas.

Any of these additional properties has a potential impact on synchronization and its dynamical properties. In the following we will first give a few examples of experiments involving classical nonlinear dynamics ideas of synchronization and then focus on a subset of four important problems of not so classical nature: (i) the synchronization in minimal neuronal networks with plastic synapses (synchronization with activity dependent coupling), (ii) synchronization of bursts that are generated by a group of nonsymmetrically coupled inhibitory neurons (heteroclinic synchronization), (iii) the

coordination of activities of two coupled neuronal networks (partial synchronization of small composite structures), and (iv) coarse grained synchronization in larger systems (synchronization on a mesoscopic scale).

II. NEW LIFE OF CLASSICAL IDEAS

Classical phenomena such as mutual synchronization, entrainment, and chaotic synchronization are now observed in many biological experiments, not only *in vitro* but also *in vivo* (see Ref. 29 for a review). We discuss below just a few such experiments and modeling results to illustrate the diversity of "new bottles for the old wine."

A. Synchrony through common input

Many automatic and voluntary behaviors require that motor commands are tightly coordinated between left and right cerebral hemispheres in vertebrates (see, for example, Refs. 30 and 31). The neuronal mechanism underlying such coordination is classical synchronization. It can be either mutual synchronization, because of direct synaptic connections between left and right hemispheres, or synchronization by common input (an external field). For example, song production in birds is a highly stereotyped, learned motor behavior that requires finely tuned coordination between hemispheres. In Ref. 32, neuronal activity was recorded simultaneously from the song control nucleus HVc in each hemisphere of singing adult male zebra finches. It was observed that the patterns of recorded multiunit activity in the two hemispheres were highly correlated during short segments of the song motor pattern.[33–35] Because the anatomic data have not revealed the presence of interhemispheric connections between the two HVcs, the observed "synchronization" evidently is a result of common inputs to both hemispheres. Motor control areas that are involved in this coordination, apparently play a dual role in controlling motor output. On one hand, output signals instruct downstream motor structures (muscles), whereas on the other hand, they transmit signals that serve to synchronize both hemispheres.

B. Mutual neuronal synchronization

Neurons can interact via inhibitory and excitatory synapses or gap junctions (ohmic electrical connections) to produce basic forms of neuronal activity, which serve as building blocks for neuronal microcircuit dynamics. The most classical example from a nonlinear dynamical systems point of view, are pairs of neurons coupled with gap junctions. Phase locking of such electrically coupled pairs of inhibitory interneurons plays an important role in the dynamics of neocortex.[36–39] Another example is the synchronization of conditionally bursting neurons with electrotonic coupling in the mammalian spinal cord.[40,41] This form of synchronization is important for the generation of stable rhythms necessary for the locomotor activity of animals. Theoretical and modeling works predict that electrical synapses promote synchronization in both phase and anti-phase modes.[42–44] More complex and somewhat nonintuitive modes of dynamical behavior also emerge that allow a large sensitivity for frequency regulation,[45,46] which can be controlled by the external stimulation.[46] It is interesting to note that all these theoretical observations originate from studying the three-dimensional (3D) neuron model proposed by Hindmarsh and Rose[47] (see below) that can account for a large variety of neuronal behaviors.

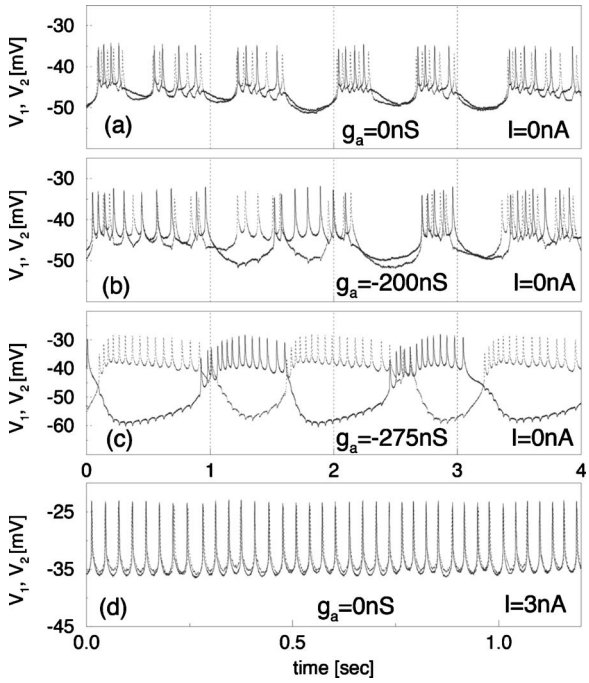

FIG. 1. Regimes of oscillations and coordination of two coupled chaotic neurons. The artificial electrotonic coupling with conductance g_a was introduced with a dynamic clamp protocol (Refs. 48–50). Depending on g_a, one can observe in-phase synchronization (a) non-synchronous states (b) and anti-phase synchronization of bursting dynamics (c). With an additional DC current injection into both of the neurons, the authors observed spike synchronization of tonic spiking (d). [First published in R. C. Elson, A. I. Selverston, R. Huerta, N. F. Rulkov, M. I. Rabinovich, and H. D. I. Abarbanel, Phys. Rev. Lett. **81**, 5692 (1998). Copyright (1998) by the American Physical Society.]

The model predictions have been verified in experiments of invertebrate *in vitro* preparations of small neuronal networks. Figure 1 shows the main regimes of coordination in a minimal network of two living chaotic cells [pyloric dilator (PD) neurons from the stomatogastric ganglion of a crustacean] coupled through an artificial electrotonic connection.[51] There are both synchronous and asynchronous regimes of activity. In this experiment the electrical synapse was built on top of the existing natural coupling between the two cells. The figure illustrates the different synchronization levels as a function of the coupling and a DC current injected into both cells. With their natural coupling ($g_a=0$) and no current injection, the two cells are synchronized and exhibit irregular spiking-bursting activity. With an artificial electrical coupling that compensates the gap-junction current, i.e., $g_a<0$, the two neurons behave independently. Increasing the negative (compensating) conductance g_a leads to a regularized anti-phase bursting activity. With no artificial coupling but an additional DC current injection into the neurons, the two neurons remain synchronized, exhibiting tonic spiking activity.[51]

Similar phenomena have been found in experiments with two pyloric central pattern generators (CPGs) connected through artificial inhibitory synapses implemented in dynamic clamp.[48,49,52] Reciprocal inhibitory coupling between the pacemaker groups [consisting of the anterior burster (AB) neuron and two pyloric dilator (PD) neurons in each CPG] leads to anti-phase synchronization while nonreciprocal coupling from the lateral pyloric neurons to the PD neurons of the other CPG produces in-phase synchronization.[53]

C. Entrainment

The third classical situation of synchronization apart from common input and mutual synchronization is entrainment of one oscillator by another. The work in Ref. 54 addresses the entrainment and the resulting coordination of two distinct periodic oscillatory central pattern generators (CPGs). As seen in many experiments, a low-frequency and low-amplitude sinusoidal current input does not worsen the precision of the intrinsic oscillation of such a CPG (the pyloric CPG of the lobster in this case); rather, a subharmonic, e.g., 1:2, 1:5, synchronization was observed (Fig. 2). Analogously, the low-frequency input from another, much slower CPG (the gastric mill CPG of the lobster) can act as a regularizing factor on the pyloric rhythm and entrain it. In these experiments, intermittent or chaotic responses were observed only in a narrow range of stimulus parameters indicating that, at least in this system, entrainment prevails over desynchronized states such that the intact pyloric CPG can maintain long-term stable oscillations.

III. SYNCHRONIZATION WITH PLASTIC SYNAPSES

A. Difficulties with synchronization through excitatory connections

Models have revealed that synchronization (entrainment) of neurons by excitatory synapses is typically less successful than by the electrotonic (ohmic) connections discussed so far. This has several reasons. To start with, the interaction is typically unidirectional because the synapse only affects the post-synaptic neuron and a reciprocal synapse may not exist. It is, furthermore, unidirectional in that the synapses delivers almost exclusively positive currents to the target neuron. While this may lead to both a speed-up or a slow-down of the postsynaptic oscillations, depending on the type of neuron, it is still a severe limitation. In addition to its unidirectionality the interaction is also intermittent because the presynaptic neuron only affects the postsynaptic cell when it fires a spike, which lasts only on the order of milliseconds compared to interspike intervals in the tens to hundreds of milliseconds. Therefore, the neurons are practically uncoupled for most of the time. Finally, the naive expectation "the stronger the coupling the better the synchronization" fails in this case as the presynaptic drive can be both too strong or too weak, and in either case synchronization fails.

Synchronization with excitatory synapses accordingly is typically poor when tested with standard models. However, in the brain, synchronization is observed in networks with abundant excitatory connectivity. It has been suggested that this surprising observation may be due to additional mechanisms at work in the brain. One candidate would be the large inhibitory neuronal populations also present in almost all brain structures, other candidates are potential homeostatic mechanisms that let neurons adapt to each other. Zhigulin *et al.*[55] suggested a third mechanism, the plasticity of synapses in form of spike timing-dependent plasticity (STDP).[56,57]

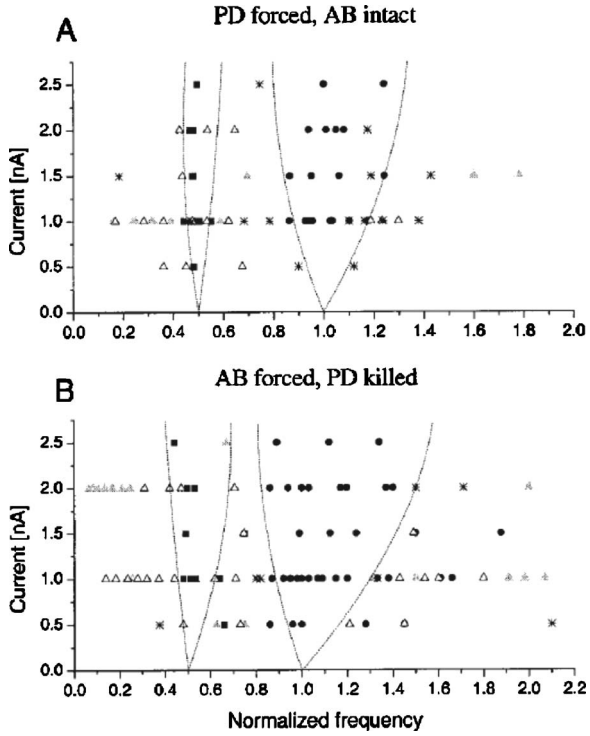

FIG. 2. Arnol'd maps for the forced intact pacemaker group of the California spiny lobster *Panulirus interruptus* and for the isolated AB pacemaker cell in the group show zones of synchronization and complex behavior. (A) stability/instability in the (A,f) plane for the bursting modes of the pacemaker neurons when forced by a sinusoidal current $I_{\sin}(t)$. The frequency f is normalized to the intrinsic bursting frequency. Symbols represent various bursting/firing modes: filled circles, 1:1 phase locking; filled squares, 1:2 phase locking; filled triangles, other $n:m$ phase-locked patterns; open triangles, quasiperiodic responses; stars, irregular/chaotic patterns. Two zones of synchronization are depicted in each panel: the 1:1 phase-locking and 1:2 phase-locking zones. (B) Responses of the isolated AB neuron. When both PD neurons were killed, the responses of the AB neuron alone led to wider zones of synchronizations than with all pacemaker neurons intact. [Reprinted from A. Szücs, R. C. Elson, M. I. Rabinovich, H. D. I. Abarbanel, and A. I. Selverston, J. Neurophysiol. **85**, 1623 (2001). Used with permission from the Journal of Neurophysiology.]

B. Synchronization with STDP synapses

Spike timing-dependent plasticity was first discovered in *in vitro* preparations of vertebrate neurons that were subjected to protocols of defined spiking patterns in a pre- and a postsynaptic cell.[56,57] Depending on the relative timing of spikes in the pre- and postsynaptic neuron, the synapse between the two neurons can either increase its conductance (potentiation), decrease it (depression) or remain unchanged.

Zhigulin *et al.*[55] simulated two neurons connected by a synapses with this STDP behavior. The neurons were described by a standard Hodgkin–Huxley[58] (H–H) neuron model,[59]

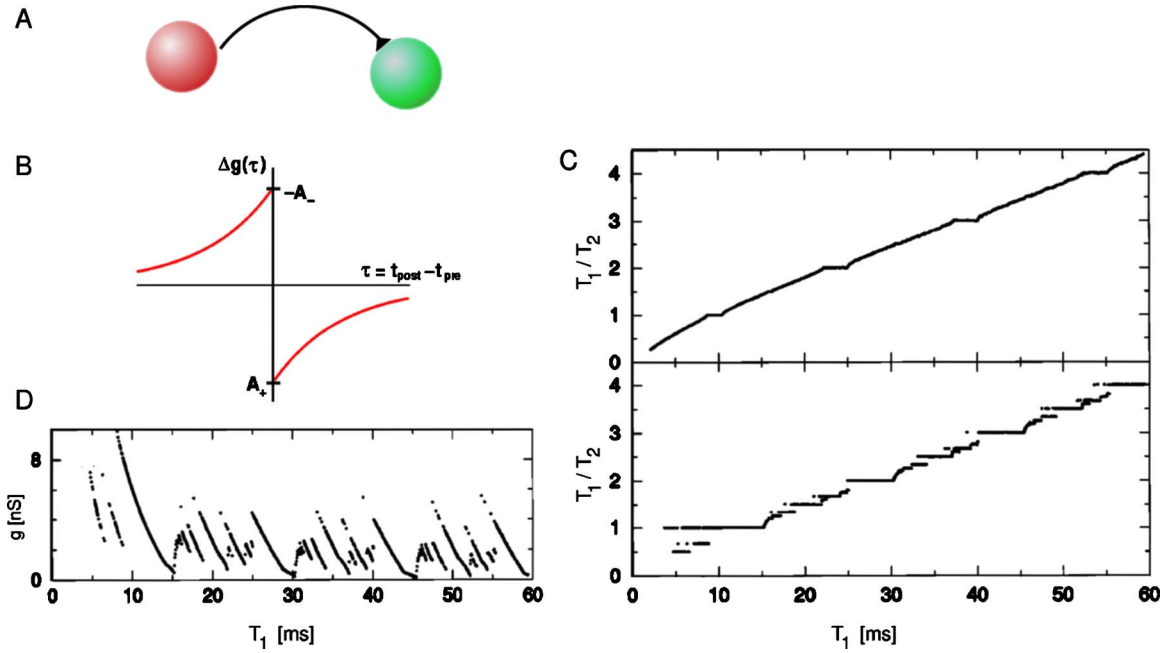

FIG. 3. (Color online) (A) Diagram of the considered system. (B) Inverse STDP rule as abstracted from the observations in the electrosensory lobe of weakly electric fish. (C) Devil's staircase illustrating the improved synchronization of neurons driven by a plastic synapse (bottom) vs those driven by a synapse of constant strength (top). (D) average synaptic strength of the driving STDP synapse for different driving period. [Modified from V. P. Zhigulin, M. I. Rabinovich, R. Huerta, and H. D. I. Abarbanel, Phys. Rev. E **67**, 021901 (2003). Copyright (2003) by the American Physical Society.]

$$C\frac{dV_i(t)}{dt} = -I_{\mathrm{Na}}(t) - I_{\mathrm{K}}(t) - I_{\mathrm{leak}}(t) - I_{\mathrm{syn}}(t) - I_{\mathrm{stim}}, \tag{1}$$

where $i=1,2$ denotes the number of the pre- and postsynaptic neuron, respectively, the leak current is given by $I_{\mathrm{leak}}(t) = g_{\mathrm{leak}}(V_i(t) - E_{\mathrm{leak}})$, and $I_{\mathrm{Na}}(t)$ and $I_{\mathrm{K}}(t)$ were[59]

$$\begin{aligned} I_{\mathrm{Na}}(t) &= g_{\mathrm{Na}} m_i(t)^3 h_i(t)(V_i(t) - E_{\mathrm{Na}}), \\ I_{\mathrm{K}}(t) &= g_{\mathrm{K}} n_i(t)^4 (V_i(t) - E_{\mathrm{K}}). \end{aligned} \tag{2}$$

I_{stim} is a constant input current forcing each neuron to spike with a constant, I_{stim}-dependent frequency, and the second neuron was driven by the first via the excitatory synaptic current I_{syn} given by Eq. (4) below. The activation and inactivation variables $y_i(t)=\{n_i(t), m_i(t), h_i(t)\}$ satisfied standard first-order kinetics (see Refs. 55 and 59). These neurons were connected by a one-directional coupling of a chemical synapse described by

$$I_{\mathrm{syn}}(t) = g(t) S(t) V_2(t), \tag{3}$$

$$\frac{dS(t)}{dt} = \alpha[1 - S(t)]H(V_1(t)) - \beta S(t), \tag{4}$$

with $H(V)=1+\tanh(10V)/4$. The coupling strength g was then subject to the inverse STDP learning rule

$$\Delta g(t) = G(\Delta t) = -A\ \mathrm{sgn}(\Delta t)\exp(-\gamma|\Delta t|), \tag{5}$$

with $A=0.004$ μS and $\gamma=0.15$ ms^{-1}, illustrated in Fig. 3(B), a type of learning that has been found in the electrosensory lobe of the weak electric fish.[60] The main results of this study are illustrated in Figs. 3(C) and 3(D). Introducing the plasticity in Eq. (5) widens the synchronization steps, in particular for 1:1 synchronization resulting in wide regions of stable 180° phase shift synchronization. The resulting steady-state coupling strength shown in Fig. 1(d) illustrates how the plasticity adjusts the strength of the synapse to an appropriate value—a small drive on the right end of each synchronization step, where the intrinsic frequencies of the two neurons are very similar, and a stronger drive on the left end, where the intrinsic frequencies differ more.

In subsequent work[61] the improvement of synchronization with excitatory synapses was generalized to synapses with "normal" STDP and in-phase synchronization with a constant (small) phase lag. The learning function in this case was given by the more standard

$$\Delta g(t) = \begin{cases} A_+ \dfrac{\Delta t - \tau_0}{\tau_+} e^{-(\Delta t - \tau_0)/\tau_+} & \text{for } \Delta t > \tau_0, \\ A_- \dfrac{\Delta t - \tau_0}{\tau_-} e^{(\Delta t - \tau_0)/\tau_-} & \text{for } \Delta t < \tau_0, \end{cases} \tag{6}$$

such that the synapses are potentiated, if a presynaptic spike arrives before a postsynaptic spike ($\Delta t>0$), and is depressed if the order is reversed ($\Delta t<0$)[56,57] [Fig. 4(B)]. The synchronization was demonstrated in a hybrid experiment in which a simulated computer neuron was driving an isolated beating cell from the mollusk *Aplysia's* abdominal ganglion. The time windows and amplitudes of potentiation and depression in the learning rule were adjusted to the time scales and size of the *Aplysia* neurons and typically chosen as $\tau_+=80$ ms, $\tau_-=120$ ms, $A_+=100$ nS, $A_-=50$ nS, and $\tau_0=30$ ms. The main results are illustrated in Fig. 4. The 1:1 synchronization region is augmented considerably by the presence of STDP [Fig. 4(C)] and the same rule of strong coupling on the left and weak coupling on the right of the synchronization regions holds. Moving the experiment into a hybrid system

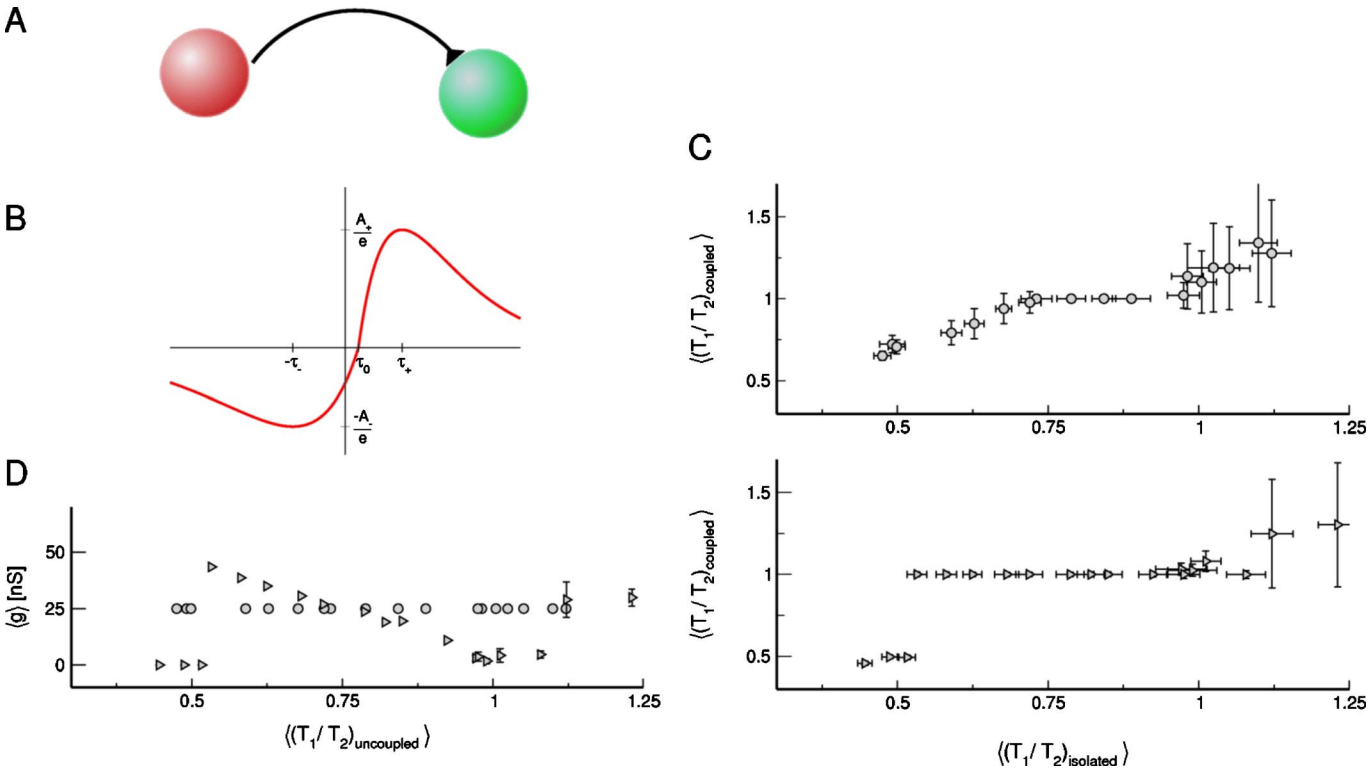

FIG. 4. (Color online) Synchronization (entrainment) of an isolated beating cell of the mollusk *Aplysia Californica* with a simulated synapse with "normal" STDP. (A) Illustration of the "circuit." (B) STDP rule used. (C) Devil's staircase showing the extended 1:1 synchronization plateau. (D) final (stationary) average synaptic strength of the STDP synapse. Note that synchronization does not only occur more often with the STDP synapse but also is more precise in a noisy environment (indicated by the much smaller error bars on the average ISIs in (C). [Data first published in T. Nowotny, V. P. Zhigulin, A. I. Selverston, H. D. I. Abarbanel, and M. I. Rabinovich, J. Neurosci. **23**, 9776 (2003).]

automatically introduced considerable amounts of noise and additional nonstationarity (e.g., short-term plasticity or homeostatic effects in the target neuron). The effect of improved synchronization proved immune against these perturbations. This work also made a clear prediction for the relationship between the learning rule and the ensuing synchronized state: The phase lag in the synchronized state should be directly linked to a shift τ_0 in the STDP learning curve of similar magnitude. This prediction was recently verified in a rather different system, the olfactory system of the locust.[62] Here, the authors found that neurons in the lobe of the mushroom body of the locust exhibit activity that is synchronized with the activity of the presynaptic intrinsic cells of the mushroom body, the Kenyon cells. This synchronization seems to be regulated and improved by STDP of the excitatory synapses from the Kenyon cells to the lobe neurons. Furthermore, they also observed the predicted small shift in the STDP learning curve, which they extracted from their paired-spike recordings.

The idea of plastic synapses improving synchronization has been taken up in several subsequent works including a study on enhancement of synchronization in neuronal ensembles[63,64] and the interaction of two neurons with less regular intrinsic activity.[65] It was also used in more applied work; e.g., for how to avoid pathological synchronization states that may have come about by the STDP of excitatory connectivity with deep brain stimulation.[66] This idea was based on the observation that besides the fully synchronized state there may be other non-synchronous stable states[67] in networks with excitatory STDP connectivity.

IV. SYNCHRONIZATION OF INHIBITORY MOTIFS

A. Ultrasubharmonic synchronization

According to the traditional view of synchronization, a weak periodic input is able to lock a nonlinear oscillator at a frequency close to that of the input (1:1 zone). If the forcing increases, it is possible to achieve synchronization at subharmonic bands as well. Rabinovich *et al.*[68] demonstrated the inverse phenomenon in a competitive dynamical system: with a weak signal the 1:1 zone is narrow, but the synchronization of ultra-subharmonics is dominant. In the system's phase space, there exists a heteroclinic contour in the autonomous regime, which is the image of sequential dynamics. Under the action of a weak periodic forcing, in the vicinity of the contour a stable limit cycle with long period appears. This results in very low-frequency oscillations that lock to the finite frequency of the forcing. It has been hypothesized that this phenomenon could be the origin for the synchronization of slow and fast brain rhythms.

1. Rate model

Figure 5 shows the synchronization bands for different strengths of the forcing in a system of three units described by

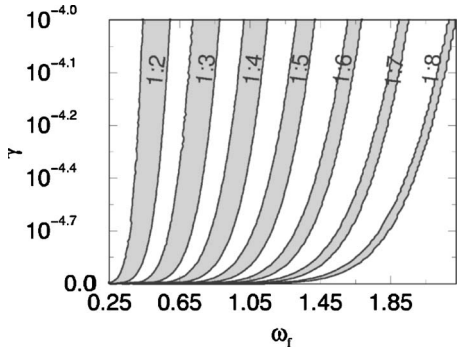

FIG. 5. Bands of synchronization in system (1) as a function of the strength of the forcing for some representative subharmonics. The parameter values were $\rho_{12}=\rho_{23}=\rho_{31}=1.25$, $\rho_{13}=\rho_{21}=\rho_{32}=0.8$, and $\varphi_1(\omega_f t,a_i)=(1-a_i)(\sin(\omega_f t)+1)$, $\varphi_2=\varphi_3=0$. [First published in M. I. Rabinovich, R. Huerta, and P. Varona, Phys. Rev. Lett. **96**, 014101 (2006). Copyright (2006) by the American Physical Society.]

$$\frac{da_i}{dt}=a_i\left[1-\left(a_i+\sum_{j\neq i}^{N}\rho_{ij}a_j\right)\right]+\xi(t)+\gamma\varphi_i(\omega_f t,a_i), \quad (7)$$

where $a_i(t)\geq 0$, $i=1,\ldots,3$ represent the rate of neuronal activity, $0\leq\rho_{ij}\leq 1$ is an inhibitory connection matrix, $\varphi_i(\omega t,a_i)\geq 0$ a periodic function with period $T=2\pi/\omega$, and $\xi(t)$ a Gaussian noise term.[68] A very small strength of the stimulus $\gamma\ll 1$, is able to induce ultrasubharmonic synchronization that remains in the presence of noise. Figure 5 shows that the widths of the synchronization bands are squeezed for $\gamma\to 0$. This figure also shows that the synchronization bands of the system, as a function of the forcing frequency, have a fairly smooth dependence on the forcing, which indicates that the system near a heteroclinic trajectory has a good degree of flexibility to lock in a wide range of ultrasubharmonics, leading to multistability.

2. H–H model

Small motifs of more realistic, spiking neurons that are coupled by inhibitory synapses can also be synchronized to an external input into one of the neurons, much like the simpler rate model. As shown recently, these small motifs implement a heteroclinic oscillator[69] that is analogous to the rate model described above and can also oscillate at many frequencies. Figure 6(A) illustrates the entrainment of such a circuit by a periodic sinusoidal driving current. The neurons were described by the Eqs. (1) and synapses from neuron i to neuron j were described by[70]

$$\frac{dR_{ij}}{dt}=\frac{1}{\tau}(-R_{ij}+\Theta(V_j-V_{\text{th}})), \quad (8)$$

$$\frac{dS_{ij}}{dt}=\frac{1}{\tau}(-S_{ij}+R_{ij}), \quad (9)$$

$$I_{ij}=g_{ij}S_{ij}(V_{\text{rev}}-V_i), \quad (10)$$

with $\tau=25$ ms, $V_{\text{th}}=-20$ mV, $V_{\text{rev}}=-80$ mV, $g_{12}=g_{23}=g_{31}=0.07$ μS, and $g_{21}=g_{32}=g_{13}=0.7$ μS. The synchronization behavior is very similar to the dynamics of an elemental strongly nonlinear oscillator like, e.g., the classic van der Pol oscillator,[71] as illustrated in Fig. 6(B).

B. Synchronization of chaotic sensory and motor networks

There are many types of neuronal networks involved in the sequential motor behavior of animals. For higher species, the control and coordination of the network dynamics is a function of the higher levels of the central nervous system, in particular the cerebellum. However, in many cases, especially for invertebrates, such coordination is the result of direct synaptic connections between small circuits; i.e., brain network motifs. It has been shown that even chaotic oscillations of such motifs can be coordinated by electrotonic synapses connecting one or several pairs of neurons that belong to two different motifs.[72]

The authors analyzed the coordination and synchronization of the sequential activity of two statocyst model networks of the marine mollusk *Clione*. The statocysts are gravity sensory organs that play a key role in postural control of the animal and the generation of a complex hunting motor program. Each network was modeled by a small ensemble of neurons with winnerless competitive dynamics based on nonsymmetric inhibitory interaction (Fig. 7). Venaille *et al.*[72] analyzed how two such networks are synchronized by electrical coupling in the presence of an external signal. It was observed that as a function of the number and the strength of connections between the two networks, it is possible to coordinate and synchronize the sequences that each network

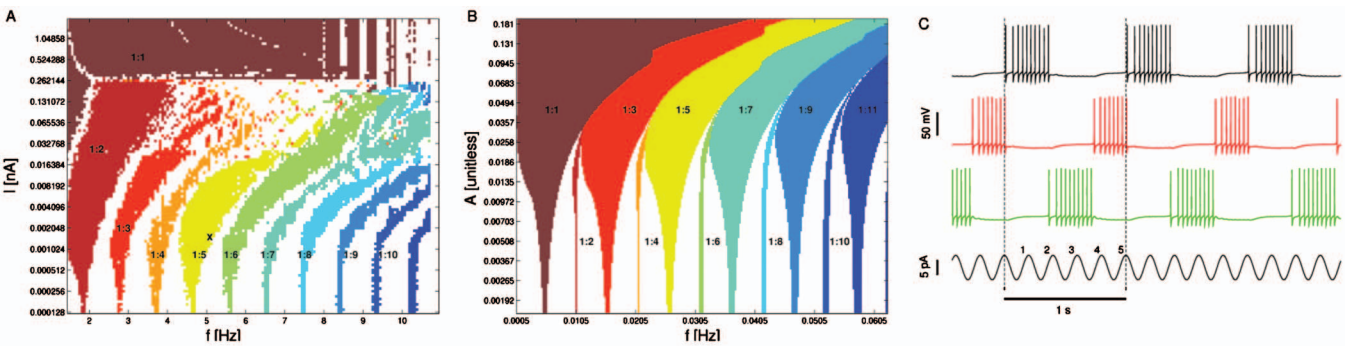

FIG. 6. (Color) Arnol'd tongues for the driven heteroclinic motif (A) and a van der Pol oscillator (B) for comparison. (C) An example of the raw data underlying (A) (marked with a cross in A).

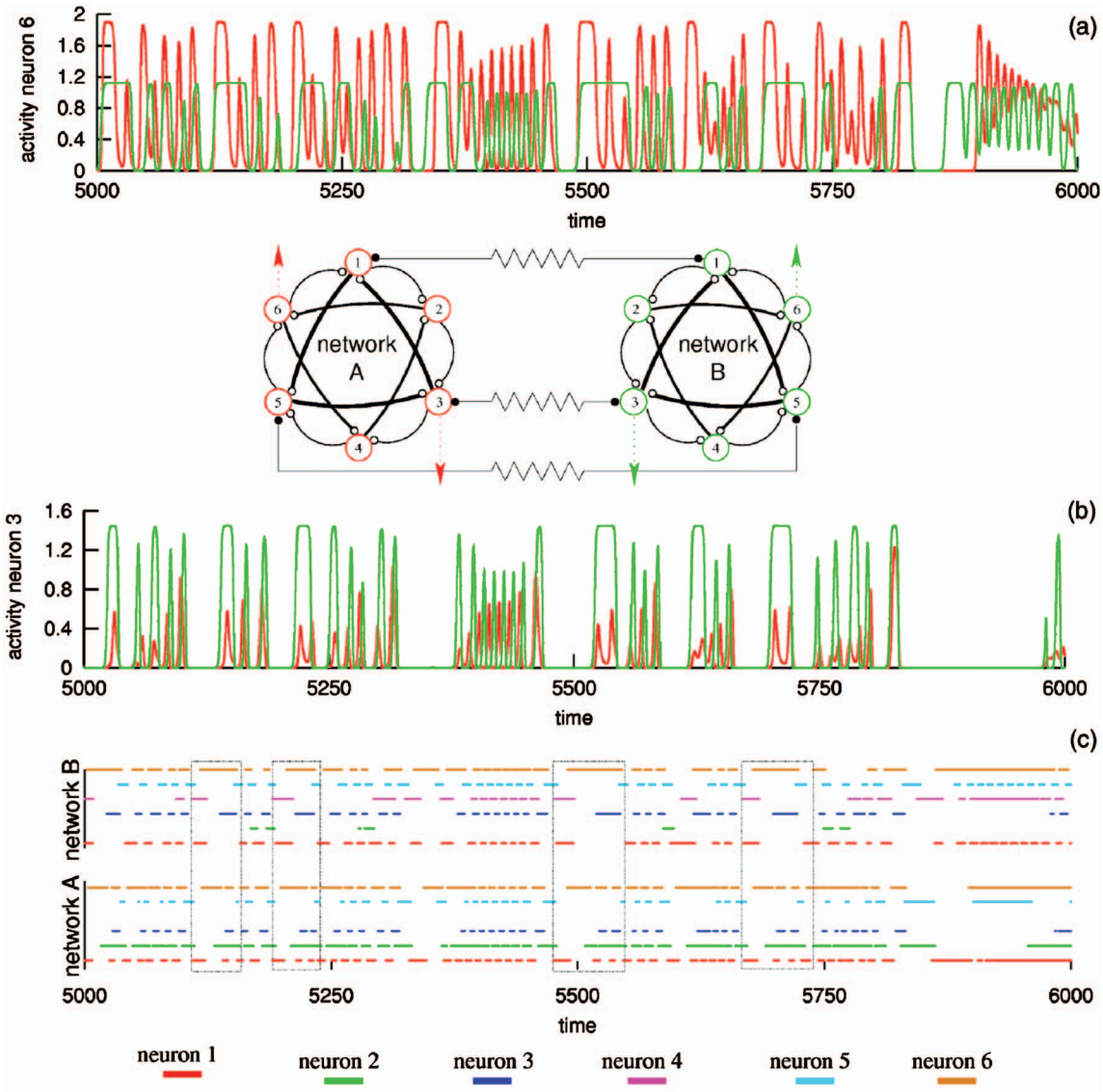

FIG. 7. (Color) Activity of the networks with three electrotonic connections between them. The coupling vector is $g=(0.01,0,0.01,0,0.01,0)$; i.e., neurons "1", "3," and "5" are connected. Panel A shows activity of neurons labeled as "6" in both networks. Panel B shows the activity of neurons labeled as "3." Panel C shows the time intervals in which each neuron is active (activity $a_i>0.03$). Note the activation sequence lock even among neurons of different networks (the dotted rectangles point out some examples). [First published in A. Venaille, P. Varona, and M. I. Rabinovich, Phys. Rev. E **71**, 061909 (2005). Copyright (2005) by the American Physical Society.]

generates with its own chaotic dynamics. In spite of the chaoticity, the coordination of the signals is established through an activation sequence lock for those neurons that are active at a particular instant of time.

C. Mutual synchronization of two H–H motifs: through excitatory or inhibitory synaptic connections

The brain contains billions of neurons that are nonlinear oscillators. As already mentioned, unlike other nonlinear media, these elemental oscillators are likely organized in small subunits, so-called brain network motifs.[63,73] A first step in analyzing synchronization, therefore, is to look at the synchronization of such small microcircuits. We have built a model of two three-neuron circuits with asymmetric connections. The neurons in the two coupled circuits are again described by Eq. (1) with connecting synapses described by

$$\frac{dS}{dt}=\alpha(1-S)F(V_{\text{pre}})-\beta S, \tag{11}$$

$$F(V)=\tfrac{1}{2}[\tanh((V-V_{\text{th}})/V_{\text{slope}})+1], \tag{12}$$

$$I_{\text{syn}}=gS(V_{\text{rev}}-V_{\text{post}}), \tag{13}$$

with $\alpha=0.5$ kHz, $\beta=0.01$ kHz, $V_{\text{th}}=-20$ mV, $V_{\text{slope}}=5$ mV, $V_{\text{rev}}=-80$ mV, $g_{12}=g_{23}=g_{31}=g_{45}=g_{56}=g_{64}=0.1$ μS, and $g_{21}=g_{32}=g_{13}=g_{54}-g_{65}=g_{46}=0.01$ nS (practically 0). In addition to these familiar asymmetric connections within the three-neuron motifs, one neuron of the "presynaptic" motif connects to one neuron of the "postsynaptic" motif with a conductance g_{14} [Fig. 8(A)], which is a control parameter. The reversal potential for the connecting synapse was

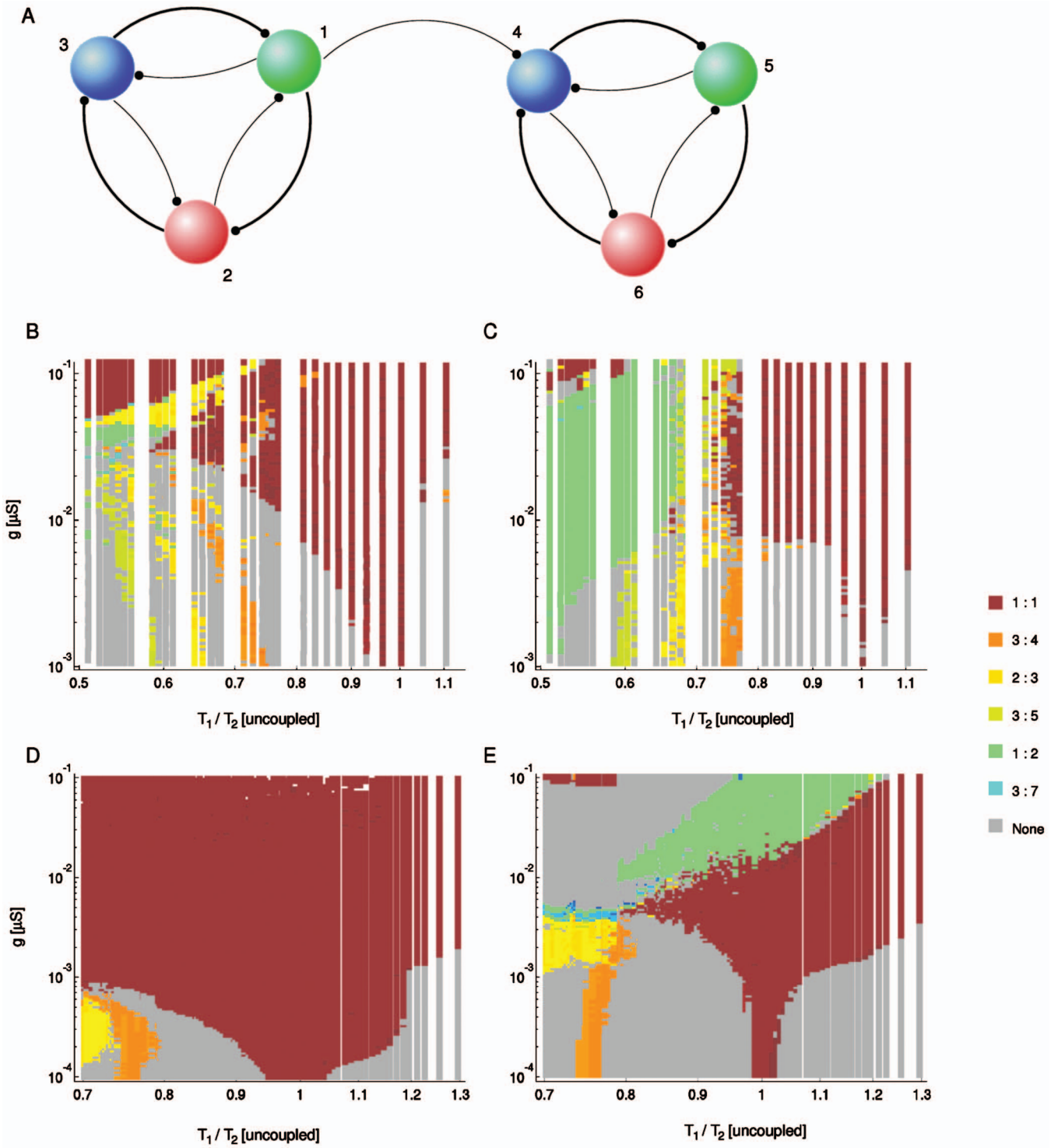

FIG. 8. (Color) Synchronization of two three-neuron motifs of H–H neurons (A, B, C) compared to the synchronization of "typical" bursting neurons (D, E), here map-based bursting neurons (Ref. 74). (A) The connectivity with strong interactions within the motifs and a weaker interaction between one of each of the motif neurons (neurons 1 and 4). (B) and (D) show the synchronization regions for excitatory coupling, while (C) and E) were obtained for inhibitory coupling.

$E_{\mathrm{rev},14}=0$ mV for an excitatory connection [Fig. 8(B)] and $E_{\mathrm{rev},14}=-80$ mV for an inhibitory coupling [Fig. 8(C)]. All neurons in the postsynaptic motif are excited by a constant $I_{\mathrm{stim}}=0.15$ nA, while all neurons of the presynaptic motif receive a stimulus current I_{stim}, which is varied in a range from 0.12 to 0.5 nA, corresponding to uncoupled period ratios of $T_1/T_2=0.5\ldots1.1$.

We observe some peculiarities immediately. Due to the presynaptic motif's own intrinsic complexity the period ratios do not vary smoothly with the injected currents leading to the white stripes of unattainable uncoupled frequency ratios in Figs. 8(B) and 8(C). In comparison between excitatory and inhibitory coupling we notice a much larger region of 1:2 synchronization for the latter. If we compare these

results to the synchronization behavior of two "generic" bursting neurons, the same difference of enhanced 1:2 synchronization appears. However, the overall synchronization regions are quite differently shaped.

The presented results show that the details of spiking activities of the neurons in the motif, in fact, do not influence the motif's interaction with other motifs as it behaves much like a more elemental oscillator. This is a very important message that supports one of the basic principles that the brain uses: the dynamics on different levels of brain complexity hierarchy that operate on different time and space scales are relatively independent (see also Ref. 69).

V. COARSE-GRAINED SYNCHRONIZATION

A. Patterns of synchronization

On a larger scale beyond neuronal network motifs, neuronal media can be seen as nonequilibrium media that generate ordered or coherent spatio-temporal structures due to the dynamical interaction between their elements, the neurons, and the intrinsic properties of these neurons. Pretchl *et al.*[75,76] reported observations of cortical oscillations in the turtle leading to linear and circular waves that are a signature of the presence of an underlying excitable nonequilibrium medium. In Refs. 77 and 78 the authors could also find the formation of coarse grain dynamics in a slide of the mammalian cortex by blocking the inhibition of the neuronal media. One of the main features of neuronal media is the existence of different time scales in the individual oscillations. These time scales produce a rich and complicated behavior that requires a coarse grained interpretation of the whole system to comprehend it. A very good system to understand the coarse grain dynamics of neuronal media is the Hindmarsh–Rose model[47] because two time scales are present in it and while it has rich dynamics including chaos it can still be expressed in a simple mathematical form. The system is built around a fast variable for the spiking dynamics combined with a slow variable that produces modulation in the spiking behavior of the neuron. The template system of ordinary differential equations (ODEs) is given by

$$\frac{dx_i}{dt} = y_i + ax_i^3 - z_i + e_i - g\sum_j (x_i - x_j),$$

$$\frac{dy_i}{dt} = b - cx_i^2 - y_i, \quad \frac{1}{\mu}\frac{dz_i}{dt} = -rz_i + rS(x_i + d),$$

where the index j runs over the nearest neighbors of the lattice where usually $S=4$, $a=3$, $d=1.6$, $b=1$, $c=5$, and r is set in the chaotic regime with value $r=0.0021$. The strength of the dissipative coupling is determined by g. Computer simulations of networks built from heterogeneous elements described by this set of ODEs and individual values for e_i indicate that cooperative behavior among the elements is able to produce large-scale coherent structures with slow periodic oscillations despite the presence of chaotic elements.[79,80]

B. Coarse grained variables

In order to understand the origin of the coherent structures in this system, the dynamics of a group has to be traced. These groups display the following type of behavior depending on g: (i) chaotic behavior which dimension increases with the number of elements for small coupling, (ii) chaotic synchronization of the slow oscillations, and (iii) complete chaotic synchronization for strong coupling.

Figure 9 illustrates the effect of the coupling onto the coarse grain size of the coherent structure that is developing in the system. The stronger the coupling is the larger is the size of the "grain." In Ref. 79 a coarse grain variable representative of this group was proposed. A new set of variables obtained from an average measure of the grain that depends on g can be built, given by

$$X(t) = \frac{1}{M}\sum_{i=1}^{M} x_i(t) = \langle x_i \rangle_{\mathrm{CG}}, \tag{14}$$

$$Y(t) = \langle y_i \rangle_{\mathrm{CG}}, \tag{15}$$

$$Z(t) = \langle z_i \rangle_{\mathrm{CG}}, \tag{16}$$

where M is the number of neurons in the cluster. To build an approximate ODE for the cluster dynamics, one can use

$$x_i(t) = X(t) + \xi_i(t;g,M), \tag{17}$$

$$y_i(t) = Y(t) + \eta_i(t;g,M), \tag{18}$$

$$z_i(t) = Z(t) + \zeta_i(t;g,M), \tag{19}$$

which are then introduced into the Hindmarsh–Rose equations to obtain

$$\frac{dX}{dt} = Y + aX^2 + ar(t;g,M) - X^3 - 3Xr(t;g,M) - Z + \epsilon, \tag{20}$$

$$\frac{dY}{dt} = -cX^2 - Y - [cr(t;g,M) - b], \tag{21}$$

$$\frac{1}{\mu}\frac{dZ}{dt} = -Z + S(X + d), \tag{22}$$

where $\epsilon = \langle e_i \rangle_{CG}$, $\langle \xi_i(t;g,M) \rangle = \langle \eta_i(t;g,M) \rangle = \langle \zeta_i(t;g,M) \rangle = 0$, and the only function that plays a role, ignoring higher order terms than ζ_i^2, is $r(t;g,M) = \langle \xi_i^2 \rangle_{CG}$.

The origin of the periodic average behavior emerging when using Eqs. (20)–(22) can be understood by a pitchfork bifurcation, where $r(t;g,M)$ is either replaced by a constant or by a periodic function that represents the type of mean field action of the neighboring elements. For sufficiently small g, $r(t;g,M)$ is nearly constant with values in the range 0.4–0.5 and only a single stable fixed point is present corresponding to steady-state behavior of the cluster (Fig. 10).

For $r(t;g,M) < R_{\mathrm{crit}}$ $(g > g_{\mathrm{crit}})$, the fixed point becomes unstable and the limit cycle in the 3D phase space of the average coarse grained system undergoes a supercritical Andronov–Hopf bifurcation to a stable limit cycle. At the

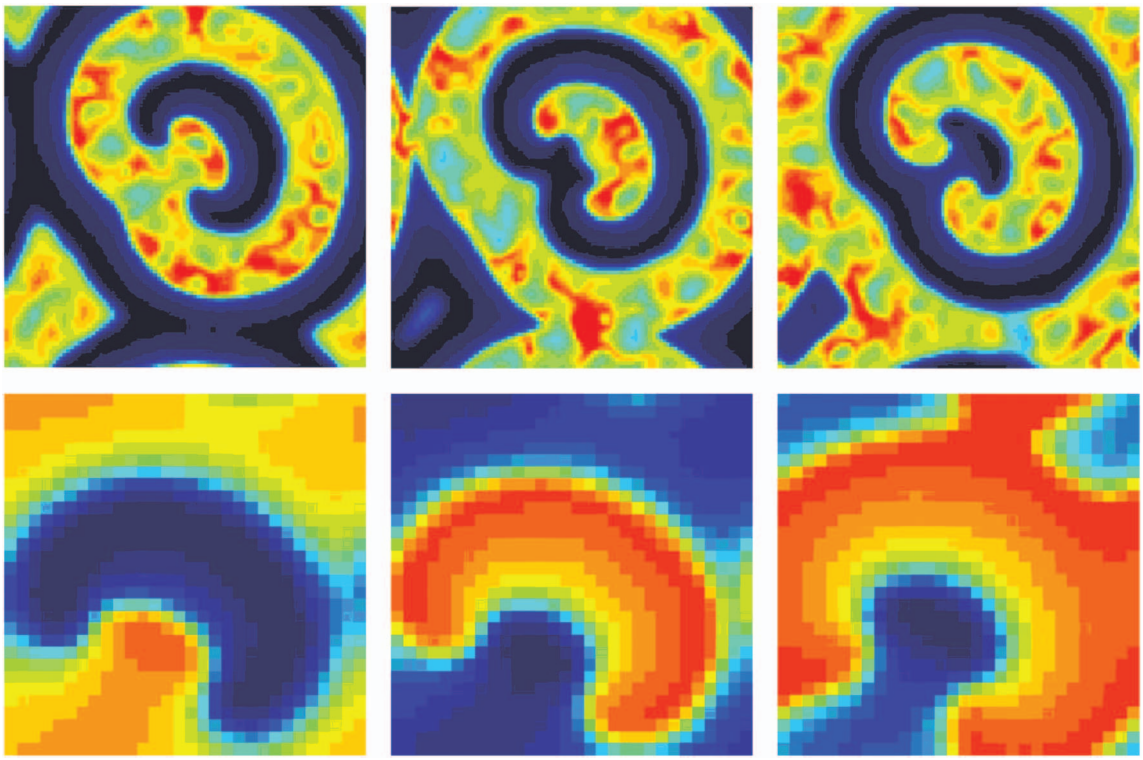

FIG. 9. (Color) The upper row represents three different snapshots of the evolution of a network of 10 000 neurons with coupling parameter, while the lower row displays the coherent structures for $g=1.5$. [Data first published in R. Huerta, M. Bazhenov, and M. I. Rabinovich, Europhys. Lett. **43**, 719 (1998).]

bifurcation point, $r(t;g,M)$ becomes a periodic function of time. Figure 11 shows an example of the limit cycle resulting from the Andronov–Hopf bifurcation.

The dynamical mechanism underlying the ordered averaged behavior of the coarse grain relies on the synchronization and regularization of the activity of the units within the grain. The degree of synchronization of a single neuron with the average activity of the whole grain depends on the strength of the coupling, as one can see on the left in Fig. 9. For regular behavior the activity of single neurons are highly synchronized with a periodic mean field that is fed into the coarse grain equations by $r(t;g,M)$. For $g=0.005$, the synchronization between mean field and individual behavior is absent and, therefore, spatio-temporal disorder prevails. The coarse grain dynamics is able to predict the bifurcation of the phenomena shown in Ref. 80 and displayed in Fig. 9. The results of the coarse grain dynamics were consistent across

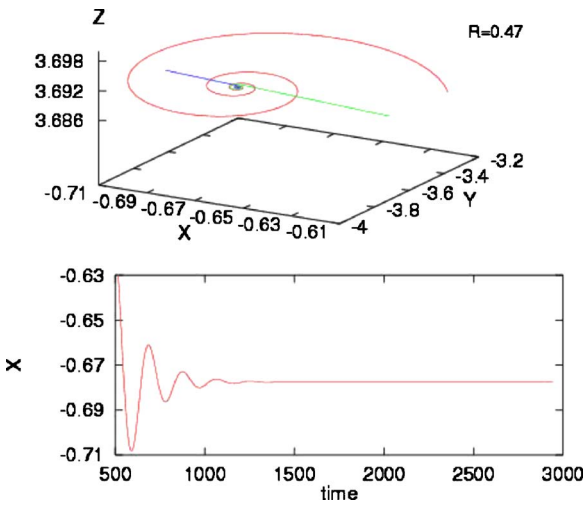

FIG. 10. (Color online) The upper plot represents the phase portrait of the coarse grained dynamics for low diffusive coupling. The lower plot shows the time course of one of the variables over time. [First published in M. I. Rabinovich, J. J. Torres, P. Varona, R. Huerta, and P. Weidman, Phys. Rev. E **60**(2), R1130 (1999). Copyright (1999) by the American Physical Society.]

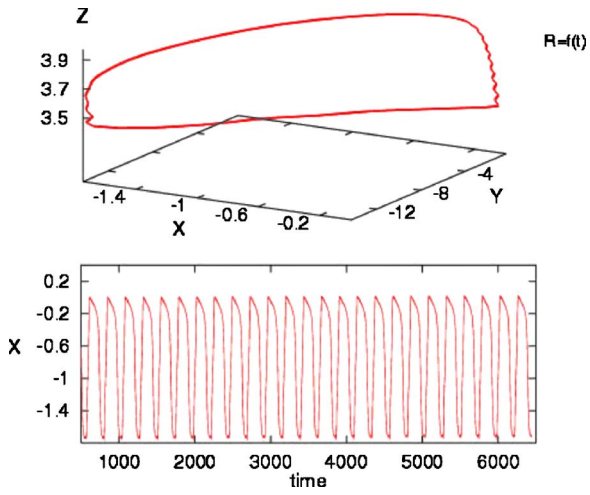

FIG. 11. (Color online) The resulting limit cycle after an Andronov–Hopf bifurcation. The function $r(t;g,M)$ was fit to simulations for a value of $g=0.1$. The lower panel shows the time series of the corresponding coarse grain dynamics. [First published in M. I. Rabinovich, J. J. Torres, P. Varona, R. Huerta, and P. Weidman, Phys. Rev. E **60**(2), R1130 (1999). Copyright (1999) by the American Physical Society.]

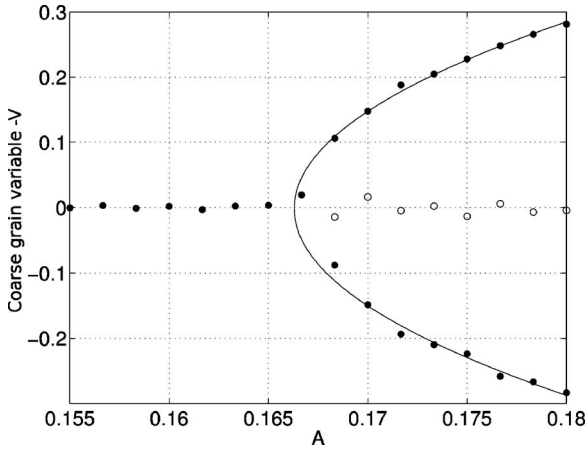

FIG. 12. The zeros of the drift term of the Fokker–Planck equation derived from the neuronal field using the coarse variable. The coarse grain variable is plotted against the gain variable of the neuronal field equations. The filled circles represent stable solutions while the open circles represent unstable ones. [Generated from data provided by C. R. Laing, first published in C. R. Laing, T. A. Frewen, and I. G. Kevrekidis, Nonlinearity **20**, 2127 (2007).]

different topologies of network connectivity. The formation of large-scale coherent structures in nonequilibrium media consisting of discrete elements with fast and slow oscillations has two key features. The first is the regularization phenomena inside clusters of chaotic elements. This regularization of the behavior is the result of the action of the averaged activity of fast pulsations in the slow coarse grain dynamics. The second feature is the instability of the homogeneous oscillation modes in a media considered to be a coarse grain lattice.

The effectiveness of the coarse grain approach for understanding the bifurcation of a complex neuronal system has also been proven to be useful in neuronal fields.[81] A neuronal field is described by a set of partial integro-differential equations

$$\frac{\partial u(x,t)}{\partial t} = -u(x,t) + \int_{-\pi}^{\pi} J(x-y) f[I + u(y,t) - a(y,t)]dy, \tag{23}$$

$$\tau \frac{\partial a(x,t)}{\partial t} = Au(x,t) - a(x,t), \tag{24}$$

on $-\pi \leq x \leq \pi$ with periodic boundary conditions as explained in Ref. 82, where $u(x,t)$ is the activity of the neurons at location x and time t and $a(x,t)$ is the intrinsic activity of the neurons. The remaining functions are the connectivity function $J(x-y)$ and the firing rate of the neurons $f(u)$, which is not spatially dependent. The approach consists in defining a new coarse scalar variable $V(t)$, which is the instantaneous difference in position between the peak of $u(x,t)$ and $a(x,t)$. Laing *et al.* assume that $V(t)$ satisfies an unknown Langevin equation and then numerically obtain the effective potential for the corresponding Fokker–Planck equation. The zeros of the drift parameter $\mu(V)$ of the Fokker–Planck equation are numerically estimated to obtain Fig. 12 by using a non-negligible level of noise. This approach is successful in predicting a pitchfork bifurcation of the neuronal media [Eq. (23)] via a coarse grain description.

VI. CONCLUSION

Reflecting one more time on the neuronal synchronization phenomena that we discussed above, an expert in nonlinear dynamical theory may say "it is very interesting, but where is the peculiarity?". Indeed, despite all the specifics of the complex biochemical processes that characterize the activity of individual elements of neuronal networks, i.e., the neurons and synapses, creating a dynamical model has become, after formalizing the problem, just another, albeit important, application of the universal tools and approaches of nonlinear dynamical theory. The answer to the question about peculiarity lies in a different aspect: The phenomena that we described in this review appear too specific, and sometimes even pathological, for the traditional models of nonlinear dynamical theory. However, for neuronal systems they are generic. This is the peculiarity. We recall here only one example: heteroclinic synchronization. It can be described in the framework of a typical rate model of neuronal information processing. Since all variables in this model are positive or equal zero by construction ($a_i \geq 0$) the phase space of the system is bounded by manifolds $a_j=0$ and, because of that, the heteroclinic sequence that exists in this system can be structurally stable. This may seem peculiar in general nonlinear dynamical theory, but for neuronal systems it is a generic phenomenon.

ACKNOWLEDGMENTS

This work was partly supported by the NIH, Grant No. R01 NS050945 (R.H., M.R.), and a RCUK fellowship (T.N.).

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